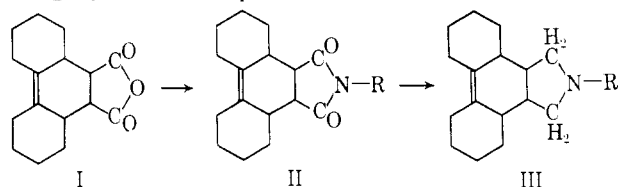


by means of lithium aluminum hydride to the base III in high yield. The product was stable to distillation



and was converted into the hydrochloride and methiodide salts.

The dihydrochloride of base III (R = dimethylaminopropyl) when screened against KB tissue culture cells was active at about 10 $\mu\text{g}/\text{ml}$. None of the compounds showed any activity against L1210 lymphoid leukemia. The dimethiodide of III (R = dimethylaminopropyl) produced ganglionic blockage when tested on the nictitating membrane of the cat and gave a moderate reduction of blood pressure in an anesthetized dog.

Experimental Section⁵

N-(3-Dimethylaminopropyl)-1,2,3,4,5,6,7,8,8a,9,10,10a-dodecahydro-9,10-phenanthrenedicarboximide (II, R = dimethylaminopropyl).—To 5 g (0.0192 mole) of finely powdered anhydride I was added, with shaking, 2.5 g (excess) of 3-dimethylaminopropylamine. After the initial reaction the mixture was heated at 180–200° for 30 min. The product distilled as a viscous glass, bp 210–220° (0.07 mm), yield 5 g (76%). *Anal.* (C₂₁H₃₂N₂O₂) C, H, N.

The monomethiodide, prepared in the usual manner, melted at 208–210°. *Anal.* (C₂₂H₃₃IN₂O₂) I.

N-(3-Dimethylaminopropyl)-3a,3b,4,5,6,7,8,9,10,11,11a,11b-dodecahydrodibenz[e,g]isoindoline (III, R = dimethylaminopropyl).—To a solution of 9 g of LiAlH₄ hydride in 1 l. of anhydrous ether, the imide II dissolved in 1 l. of anhydrous ether was added rapidly with vigorous stirring and the mixture was refluxed 4 hr. While stirring, the reaction mixture was decomposed by the dropwise addition of H₂O (36 ml) and the stirring was continued for an additional 3 hr. After standing overnight the solution was filtered and the inorganic cake was washed (dry Et₂O). The solution was dried (Na₂SO₄), the solvent was removed, and the residual oil was distilled, bp 160–170° (0.07 mm). The distillate weighed 3.3 g (80%). *Anal.* (C₂₁H₃₀N₂) C, H, N.

The dihydrochloride prepared in the usual manner after recrystallization from EtOH–Me₂CO melted at 305–306° (put in bath at 290°). *Anal.* (C₂₁H₃₀Cl₂N₂) Cl, N.

The dimethiodide was prepared in EtOH by refluxing with excess MeI and diluting with 3 vol. of EtOAc. After recrystallization from EtOH–Me₂O with a trace of ether the crystals melted at 240–242° dec. *Anal.* (C₂₃H₄₂I₂N₂) I, N.

N-(2-Dimethylaminoethyl)-3a,3b,4,5,6,7,8,9,10,11,11a,11b-dodecahydrodibenz[e,g]isoindoline (III, R = dimethylaminoethyl) was prepared as outlined above except that the imide was not distilled. The crude imide was dissolved in ether and reduced (LiAlH₄, bp 155–160° (0.05 mm)). *Anal.* (C₂₀H₃₄N₂) C, H, N.

The dihydrochloride, prepared in the usual way, melted at 259–260° dec. *Anal.* (C₂₀H₃₆Cl₂N₂) Cl.

The dimethiodide prepared as described above melted at 241–242° dec. *Anal.* (C₂₂H₄₀I₂N₂) I.

N-(3-Morpholinopropyl)-3a,3b,4,5,6,7,8,9,10,11,11a,11b-dodecahydrodibenz[e,g]isoindoline (III, R = morpholinopropyl) was prepared as above from 5 g of the anhydride without isolation of the imide. It boiled at 180–190° (0.07 mm) and weighed 4.1 g. *Anal.* (C₂₃H₃₈N₂O) C, H, N.

The dihydrochloride when recrystallized from EtOH–Et₂O melted at 286–289°. *Anal.* (C₂₃H₄₀Cl₂N₂O) Cl, N.

The dimethiodide was prepared in MeOH and precipitated with EtOAc. When recrystallized from EtOH–ether it melted at 246–248°. *Anal.* (C₂₅H₄₄I₂N₂O) I, N.

(5) Melting points were determined with a Thomas-Hoover apparatus and are corrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.3% of the theoretical values.

The Ethyl Homologs of 2,4,5-Trimethoxyphenylisopropylamine

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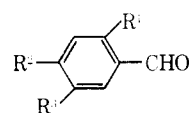
Revised Manuscript Received August 23, 1967

Of the six possible 1-(trimethoxyphenyl)-2-amino-2-propanes (trimethoxyamphetamines),¹ the 2,4,5 isomer (IIa) was the most potent as a psychotomimetic agent,^{2,3} and it serves in this present report as the reason for the synthesis of the seven possible ethyl homologs. These have been prepared by routes which preclude isomer contamination. In preliminary observations only the 4-monoethoxy isomer IIc exceeds IIa in psychotomimetic potency.

Experimental Section

The 2-ethoxy homolog (IIb) was prepared by the Claisen rearrangement of allyl 3,4-dimethoxyphenyl ether as described earlier.¹ The remaining isomers (IIc–h) employed the three separate 3,4-dialkoxyphenols obtained by the peracetic acid oxidation of the appropriate aldehyde. The synthesis of 2,4-dimethoxy-5-ethoxyphenylisopropylamine (IIc) is typical. The malononitrile derivatives were prepared as described earlier.¹ The microanalyses of all new compounds in Tables I and II are listed in Table III; melting points were determined on a Koffler Heizbank and are corrected.

TABLE I



| R ¹ | R ² | R ³ | Mp, °C (uncorr) | ArCHO C(CN) ₂ |
|--------------------------------|--------------------------------|--------------------------------|------------------|-----------------------------|
| H | OCH ₃ | OCH ₃ | 45 ^a | 147 ^b |
| H | OCH ₃ | OC ₂ H ₅ | 50 ^c | 142 |
| H | OC ₂ H ₅ | OCH ₃ | 60 ^d | 141 |
| H | OC ₂ H ₅ | OC ₂ H ₅ | Oil ^e | 105 ^f |
| OCH ₃ | OCH ₃ | OC ₂ H ₅ | 108 ^g | 136 |
| OCH ₃ | OC ₂ H ₅ | OCH ₃ | 109 ^h | 172 |
| OCH ₃ | OC ₂ H ₅ | OC ₂ H ₅ | 89 | 157 |
| OC ₂ H ₅ | OCH ₃ | OC ₂ H ₅ | 111 | 158 |
| OC ₂ H ₅ | OC ₂ H ₅ | OCH ₃ | 99 | 173 |
| OC ₂ H ₅ | OC ₂ H ₅ | OC ₂ H ₅ | 95 ⁱ | 170 |

^a L. Gattermann [*Ann.*, **357**, 313 (1907)] reported mp 43–44°. ^b H. Kauffmann [*Ber.*, **52**, 1422 (1919)] reported mp 147°. ^c E. Spath and E. Bernhauer [*ibid.*, **58**, 200 (1925)] reported mp 150–151°. ^d F. Tiemann [*ibid.*, **8**, 1127 (1875)] reported mp 64–65°. ^e Obtained from the Eastman Kodak Co. ^f R. P. Maricella and J. M. Bauer [*J. Org. Chem.*, **23**, 120 (1958)] reported mp 104–104.5°. ^g F. S. H. Head and A. Robertson [*J. Chem. Soc.*, 2434 (1930)] reported mp 110°. ^h Lit.² mp 110°. ⁱ W. Will [*Ber.*, **16**, 2106 (1883)] reported mp 95°.

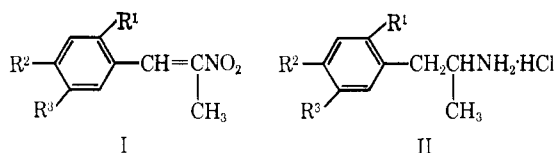
1,3-Dimethoxy-4-ethoxybenzene.—To a solution of 4-ethoxy-3-methoxyphenol in MeOH (14 g in 20 ml) was added a solution of 5.3 g of KOH in MeOH (100 ml), followed by MeI (11.9 g). The mixture was refluxed for 2 hr, quenched with 3 vol of H₂O, and made strongly basic with 5% NaOH. Extraction with ether and evaporation of the pooled extracts yielded the title ether as a clear oil, 9.7 g, *n*_D²⁰ 1.5210.

(1) A. T. Shulgin, *J. Med. Chem.*, **9**, 445 (1966).

(2) A. T. Shulgin, *Experientia*, **20**, 306 (1964).

(3) C. Nardjo, T. Sargent, and A. T. Shulgin, unpublished data.

TABLE II



| | R ¹ | R ² | R ³ | Nitrostyrene (I) | | | II | |
|---|--------------------------------|--------------------------------|--------------------------------|------------------|--------|----------|--------|----------|
| | | | | Mp, °C | Color | Yield, % | Mp, °C | Yield, % |
| a | OCH ₃ | OCH ₃ | OCH ₃ | 102 | Yellow | 83 | 181 | 92 |
| b | OC ₂ H ₅ | OCH ₃ | OCH ₃ | 76 | Yellow | 73 | 172 | 67 |
| c | OCH ₃ | OCH ₃ | OC ₂ H ₅ | 97 | Yellow | 27 | 172 | 74 |
| d | OC ₂ H ₅ | OCH ₃ | OC ₂ H ₅ | 86 | Orange | 36 | 164 | 76 |
| e | OCH ₃ | OC ₂ H ₅ | OCH ₃ | 129 | Orange | 52 | 172 | 70 |
| f | OC ₂ H ₅ | OC ₂ H ₅ | OCH ₃ | 113 | Orange | 72 | 159 | 62 |
| g | OCH ₃ | OC ₂ H ₅ | OC ₂ H ₅ | 91 | Orange | 38 | 180 | 75 |
| h | OC ₂ H ₅ | OC ₂ H ₅ | OC ₂ H ₅ | 92 | Yellow | 40 | 168 | 74 |

TABLE III
ANALYSES

| Compound | Formula | Calcd, % | | | Found, % | | |
|--------------------------------------|---|----------|------|-------|----------|-----|------|
| | | C | H | N | C | H | N |
| Benzaldehyde | | | | | | | |
| 4,5-Diethoxy-2-methoxy- | C ₁₂ H ₁₆ O ₄ | 64.27 | 7.19 | ... | 64.4 | 7.0 | ... |
| 2,5-Diethoxy-4-methoxy- | | | | | 64.5 | 7.1 | ... |
| 2,4-Diethoxy-5-methoxy- | | | | | 64.3 | 7.3 | ... |
| Benzylidenemalononitrile | | | | | | | |
| 5-Ethoxy-4-methoxy- | C ₁₃ H ₁₂ N ₂ O ₂ | 68.41 | 5.30 | 12.27 | 68.2 | 5.2 | 12.1 |
| 4-Ethoxy-5-methoxy- | | | | | 68.2 | 5.1 | 11.9 |
| 2,4-Dimethoxy-5-ethoxy- | C ₁₄ H ₁₄ N ₂ O ₃ | 65.11 | 5.46 | 10.85 | 65.1 | 5.4 | 10.7 |
| 2,5-Dimethoxy-4-ethoxy- | | | | | 64.9 | 5.2 | 10.7 |
| 4,5-Diethoxy-2-methoxy- | C ₁₃ H ₁₆ N ₂ O ₃ | 66.16 | 5.92 | 10.29 | 66.0 | 5.9 | 10.1 |
| 2,5-Diethoxy-4-methoxy- | | | | | 66.0 | 5.7 | 10.3 |
| 2,4-Diethoxy-5-methoxy- | | | | | 65.9 | 5.7 | 10.1 |
| 2,4,5-Triethoxy- | C ₁₆ H ₁₈ N ₂ O ₃ | 67.12 | 6.34 | 9.78 | 67.1 | 6.3 | 9.6 |
| Phenylnitropropene | | | | | | | |
| 2-Ethoxy-4,5-dimethoxy- | C ₁₃ H ₁₇ NO ₃ | 58.42 | 6.41 | 5.24 | 58.3 | 6.5 | 5.2 |
| 5-Ethoxy-2,4-dimethoxy- | | | | | 58.3 | 6.3 | 5.1 |
| 4-Ethoxy-2,5-dimethoxy- | | | | | 58.2 | 6.3 | 5.2 |
| 2,5-Diethoxy-4-methoxy- | C ₁₄ H ₁₉ NO ₃ | 59.77 | 6.81 | 4.98 | 59.7 | 6.7 | 5.0 |
| 2,4-Diethoxy-5-methoxy- | | | | | 59.5 | 6.7 | 4.8 |
| 4,5-Diethoxy-2-methoxy- | | | | | 59.5 | 6.7 | 4.9 |
| 2,4,5-Triethoxy- | C ₁₅ H ₂₁ NO ₃ | 61.00 | 7.17 | 4.74 | 60.9 | 7.1 | 4.6 |
| Amphetamine hydrochloride | | | | | | | |
| 2-Ethoxy-4,5-dimethoxy- | C ₁₃ H ₂₂ NO ₃ Cl | 56.62 | 8.04 | 5.08 | 56.3 | 7.9 | 5.0 |
| 4-Ethoxy-2,5-dimethoxy- | | | | | 56.2 | 7.9 | 5.0 |
| 5-Ethoxy-2,4-dimethoxy- ^a | | | | | 55.9 | 7.9 | 4.9 |
| | | | | | 55.9 | 7.9 | 5.0 |
| 2,4-Diethoxy-5-methoxy- | C ₁₄ H ₂₄ NO ₃ Cl | 58.02 | 8.35 | 4.83 | 57.7 | 8.3 | 4.7 |
| 2,5-Diethoxy-4-methoxy- ^a | | | | | 57.4 | 8.3 | 4.7 |
| 4,5-Diethoxy-2-methoxy- | | | | | 57.6 | 8.3 | 4.7 |
| 2,4,5-Triethoxy- | C ₁₅ H ₂₆ NO ₃ Cl | 59.30 | 8.63 | 4.61 | 59.2 | 8.6 | 4.5 |

^a These had rather low carbon values and were both analyzed by umr (A-60, in D₂O) and both appeared to be without contaminants.

2,4-Dimethoxy-5-ethoxybenzaldehyde.—A mixture of N-methylformanilide and POCl₃ (17.3 g in 19.6 g) was allowed to stand at room temperature for 0.5 hr. There was then added 9.2 g of the above ether and this mixture was heated for 2 hr on the steam bath. The resulting black viscous product was poured onto 800 ml of cracked ice and allowed to stand overnight. The crude aldehyde was removed by filtration and was recrystallized from 100 ml of MeOH to yield 8.8 g of fluffy white crystals.

The crude reaction product of this synthesis, as well as of each of the other five parallel Vilsmeier preparations, was subjected to glpc analysis. Two separate substrate systems were employed, a 300 × 1 cm column containing 5% 710 Silicone on 60-80 firebrick and a 150 × 1 cm column with 15% ethylene glycol succinate on 60-80 acid-washed Chromosorb W. In no case was an isomeric aldehyde evident in excess of 2% although N-methylformanilide consistently appeared to the extent of several per cent. The recrystallization step in every case effectively removed these contaminants.

1-(2,4-Dimethoxy-5-ethoxyphenyl)-2-nitropropene (Ic).—A solution of 2,4-dimethoxy-5-ethoxybenzaldehyde in AcOH (6.7 g in 25 g) was treated with 2.1 g of NH₄OAc followed by 3.3 g of nitroethane. The mixture was heated on the steam bath for 2 hr. After cooling, the addition of a small amount of water caused the deposition of the product as a thick gel which was separated by recrystallization from toluene. As noted in Table II, where both the yields and the physical properties of these nitropropenes are shown, all compounds with a 5-ethoxy group were obtained in poor yields in this nitroethane coupling step.

2,4-Dimethoxy-5-ethoxyphenylisopropylamine (IIc).—The nitrostyrene Ic, as well as all others in this study, was reduced by the Soxhlet technique employed by Ramirez and Burger⁴ with the work-up modification described earlier.¹ Again, the yields and properties are recorded in Table II.

(4) F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2782 (1950).